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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Krotz, et al

Confirmation No.: 1518

Application No.: 09/032,972

Group Art Unit: 1623

Filing Date: February 26, 1998

Examiner: Lawrence E. Crane

For: Methods For Synthesis Of Oligonucleotides

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MS Appeal Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF REPLY BRIEF PURSUANT TO 37 CFR § 1.193

Transmitted herewith in triplicate is the REPLY BRIEF in this application with respect to the Examiner's Answer dated November 4, 2003.

If any fee is required, please charge Deposit Account No. 23-3050. A duplicate of this transmittal is attached.

Date: December 16, 2003

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#39



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Sir:

APPELLANT'S REPLY BRIEF PURSUANT TO 37 C.F.R. § 1.193

Appellants submit this Reply in response to the Examiner's Answer dated November 4, 2003 in connection with the above-identified application. As discussed in greater detail below, the rejections based on 35 U.S.C. § 103(a) are improper and should be withdrawn.

Applicant's invention is directed to methods of synthesis of linear oligonucleotides and other phosphorus-linked oligomers that utilize inter alia a novel deprotection scheme that offers advantages over conventional synthetic schemes (page 6, line 30 to page 7, line 34). One key advantage is the avoidance of dichloromethane and dichloroethane solvents in the deprotection scheme (Id.) The use of such solvents pose a barrier to relatively large scale synthesis of oligonucleotides because of disposal and efficiency issues (page 6, lines 18-28). The methods of the invention comprise the steps of attaching a 5'-O-protected nucleoside to a solid support; deprotecting the 5'-hydroxyl of the nucleoside with a protic acid in a solvent that consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent; reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a covalent linkage therebetween; and then oxidizing or sulfurizing the covalent linkage (page 6, line 32 to page 7, line 13). The post solid support coupling steps are repeated at least once for subsequent couplings of additional activated phosphorus compounds (page 7, lines 14-

17). At the conclusion of the synthesis, the oligomer is cleaved from the solid support (page 7, line 18).

First Issue-- There is no basis for the rejection of Applicant's claims for obviousness over the recited multiple combination of references.

The Examiner has not demonstrated that the subject matter of claims 1-42 would have been obvious to those of ordinary skill in the art over U.S. Patent No. 5,705,621 ("Ravikumar", assigned to the owner of the instant patent application) in view of U.S. Patent No. 4,973,679 ("Caruthers") and further in view of U.S. Patent No. 5,548,076 ("Froehler") and further in view of Sproat et al. (PTO-892 Ref. W), Conway, et al. (PTO-892 Ref. Y), Atkinson et al. (PTO-892 Ref. Z), and Sproat et al. (PTO-892 Ref. RA). There is no evidence, absent Applicant's blueprint, of motivation for one skilled in the art to combine the art in the manner suggested by the examiner. Given this lack of evidentiary support, the rejection for alleged obviousness should be withdrawn.

To establish *prima facie* obviousness, the PTO must provide objective - not speculative - evidence that the knowledge generally available in the art at the time of the invention contains some suggestion or incentive that would have motivated those of ordinary skill in the art to select multiple references and to combine their teachings, and such evidence must be set forth explicitly. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Rouffett*, 149 F.3d 1350, 1359 (Fed. Cir. 1998)(stating that "the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."). As admitted in the Examiner's Answer, none of the primary references (Ravikumar, Caruthers, and Froehler) disclose the solvent of the Applicant's invention (page 5). The Examiner attempts to use the lack of disclosure of the instant solvents in the primary references as showing that the prior art was "open to all possibilities" (page 11) Applicants assert that no evidence of this intent exists. Ravikumar merely describes the state of the art that the instant invention improves upon. Caruthers was said to teach the use of "any solvent which will dissolve the reactants" (*Id.*) This teaching, however, is clearly in the context of the coupling step **not the deprotection step**. The Froehler reference also does not motivate the selection of the solvents used in the instant invention for the deprotection step. Froehler merely states that other deprotection

procedures are known to one skilled in the art. It clearly does not follow that the instantly used solvents would be selected by one skilled in the art.

The Examiner attempts to show motivation to use the instant solvents in the methods of the primary references by alleging that the Sproat, Conway, and Atkinson references show that the intermediates of the instant methods are soluble in toluene and benzene and that these solvents were "available to be selected by the ordinary practitioner during routine experimentation" (page 12). Applicants submit that solubility is but one of many factors used in the selection of a reaction solvent. Nothing in the art demonstrates or suggests that these solvents would be effective in the instantly claimed methods. At most, such evidence is obvious to try argument and lacks the legally required motivation for support of an obviousness rejection.

Finally, the Examiner states that "applicant has as yet not provided any sworn showing in support of unexpected results." Applicants submit that there is no requirement to provide such a statement and that no such showing is needed to establish the patentability of the instant claims.

The Examiner has failed to establish obviousness because there is no specific, credible evidence that those of ordinary skill in the art would have been motivated to select the cited references and to combine their teachings. Accordingly, the rejection for alleged obviousness is improper and should be withdrawn.

Second Issue-- There is no basis for the rejection of Applicant's claims over Horn et al., Nucleic Acids Research 1989, 17, 6959-6967 ("Horn WA"), in view of Horn et al., Nucleosides and Nucleotides, 25, 4842-4849 (1997) ("Horn UA").

The Examiner has not demonstrated that the subject matter of claims 1 -42 would have been obvious to those of ordinary skill in the art over Horn et al., Nucleic Acids Research 1989, 17, 6959-6967 ("Horn WA"), in view of Horn et al., Nucleosides and Nucleotides, 25, 4842-4849 (1997) ("Horn UA"). There is no evidence of record indicating that persons of ordinary skill would have been motivated to combine the teachings of the cited references, or that such persons would have been motivated to combine the references' teachings in the manner the Examiner proposes. In fact, the available evidence indicates that those of ordinary skill in the art would not have been motivated to make the combination or that such a combination would produce the invention of any instant claim. Given this lack of

evidentiary support, the rejection for alleged obviousness is improper and should be withdrawn.

The UA reference discloses use of toluene/ CH_2Cl_2 deprotection solvent, not the solvent of the instant claims. The Examiner alleges that the claim language "the solvent consists essentially of an aromatic solvent ... or an aromatic ether solvent" allows for the use of the CH_2Cl_2 containing solvent of the cited art (pages 13-14). "Consisting essentially of" is a legal term of art which means that the claim includes the element(s) set forth therein, and any unlisted elements "that do not materially affect the basic and novel properties of the invention." *PPG Indus. v. Guardian Indus. Corp.*, 156 F.3d 1351 (Fed. Cir. 1998). To accept the Examiner's view, one would have to believe that the use of CH_2Cl_2 would not materially affect the method of the invention. This conclusion would be contrary known importance of the solvent system to the synthetic methods. See, for example, the discussion of page 14 of the Examiner's Answer.

The Examiner attempts to cure the defect of the UA reference discussed in the previous paragraph by use of the WA reference. The WA reference, however, is directed to branched, not linear, oligomers. The Examiner's Answer states that because dichloroacetic acid/toluene solvent was effective in the synthesis of branched DNAs, it would be an effective solvent system in the synthesis of linear oligonucleotides (page 14). The cited art does not suggest this. The WA reference clearly disclosed the use of toluene solvent in the context of branched oligomers (see Appeal Brief at page 8). A conclusion that this solvent selection is desirable for the synthesis of linear oligomers is possible only with the benefit of the disclosures of the instant invention.

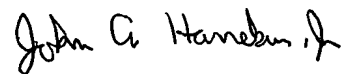
Finally, the Examiner's answer asserts that the WA reference shows that use of standard deprotecting conditions is ineffective not inoperative with branched DNAs (page 14). The distinction is of no importance. Using either characterization, the WA reference shows that the methods used therein were related to deprotection issues with **branched** oligomers not **linear** oligomers. The WA reference does not show or suggest application to linear oligomers.

The Examiner has failed to establish obviousness because there is no specific, credible evidence that those of ordinary skill in the art would have been motivated to select the cited references and to combine their teachings. Accordingly, the rejection for alleged obviousness is improper and should be withdrawn.

Conclusion

The present claims meet all requirements for patentability. As demonstrated herein and in our Appeal Brief, both of the outstanding rejections fall well short of the standard required for an obviousness rejection. Applicants ask that this patent application be remanded with an instruction to both withdraw the outstanding rejections and allow the appealed claims.

Respectfully submitted,



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